REMARKS

Reconsideration is respectfully requested.

Claims 1-9 have been cancelled. Claims 10-15 have been added. The inventorship remains unchanged in view of the amendments to the claims. No new matter has been added by way of these amendments. Support for the amendments can be found in the previously presented claims and the specification.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Interview Summary

With respect to the issue of utility, after discussing the nature of the invention it was agreed that amending the claims to recite screening of designed polypeptides for desired properties would facilitate resolution of the issue of utility. With respect to the art rejection, Applicant emphasized the difference between the method of the invention and the Topham reference and maintained that Topham should not be grounds for rejection of the present invention.

Claim Rejections – 35 USC § 112, second paragraph

A. Claims 4-8 have been rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The new claims are not indefinite.

B. Claim 4d): The Examiner states, "the phrase 'ranking secondary library' is not clear. Specification [sic] does not discuss what kind of 'ranking' is applied to the secondary library (ranking is discussed with respect to 'primary libraries')."

The term ranking is discussed with respect to secondary libraries. For example, the present specification expressly states that secondary library may be rank-ordered, and further describes various ways in which the secondary library can be ranked:

> Alternatively, in a preferred embodiment, the secondary library is also in the form of a rank ordered list. This may be done for several reasons, including the size of the secondary library is still too big to generate experimentally, or for predictive purposes. This may be done in several

> ways. In one embodiment, the secondary library is ranked using the scoring functions of PDA to rank the library members. Alternatively, statistical methods could be used. For example, the secondary library may be ranked by frequency score; that is, proteins containing the most of high frequency residues could be ranked higher, etc. This may be done by adding or multiplying the frequency at each variable position to generate a numerical score. Similarly, the secondary library different positions could be weighted and then the proteins scored; for example, those containing certain residues could be arbitrarily ranked.
> Page 27, second full paragraph.

The specification further refers to ranking secondary libraries in other passages in the specification. For example, the specification further refers to ranking secondary libraries in the discussion of shuffling:

> [i]n a preferred embodiment, the secondary library is done by shuffling the family (e.g. a set of variants); that is, some set of the top sequences (if a rank-ordered list is used) can be shuffled, either with or without error-prone PCR.
> Page 30, first full paragraph.

Therefore, the specification specifically describes ranking the secondary library, contrary to the position of the Examiner. Based on this disclosure, ranking secondary libraries is neither vague nor indefinite.

Applicants note that ranking is also used to describe primary libraries. One of ordinary skill in the art of computational methods for designing protein variants, would recognize that the disclosure of "ranking" primary libraries would also be applicable to "ranking" secondary libraries.

Applicants respectfully request that this ground for rejection be withdrawn.

D. Claims 4 and 9 are rejected for the term "as primary sequences" being unclear. New claims 10-15 are not unclear. The new claims do not constitute a narrowing amendment, and merely make explicit that which was already implicit in the claims.

E. The Examiner states:

> [it] is not clear [if] the secondary library (i.e. the library preceding the tertiary library) is formed by a random combining of residues of a probability distribution table; what relation, if any, it has to the primary sequences?

The relationship between tertiary and primary libraries is clear from the context of the claims. The "primary library" is generated with a computer program in step b). A plurality of the amino acid residues in a plurality of variant positions in the primary library are combined in step d) to generate a "secondary library." At least one unfavorably ranked sequence in the secondary library is eliminated in step e) to generate a "tertiary library." The relationship between the primary library, secondary library, and tertiary library are therefore clear from the context of the claim.

Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections – 35 USC §§ 101/112, first paragraph

Claims 4-9 are rejected under 35 USC § 101 as not supported by either a specific asserted utility or a well-established utility. Applicants have cancelled claims 4-9, rendering this rejection moot. In light of the interview summary above and new claims 10-15, Applicants believe that the application is now in condition for allowance.

Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections – 35 USC § 102 and 103(a)

Claims 4-9 are rejected under 35 USC § 103(a) as being unpatentable over Topham (J. Mol. Biol., 1993).

Topham must teach every limitation of the claimed invention. The claims are not obvious over Topham because the reference does not teach every limitation of the claimed invention.

The section pointed out by the Examiner does not teach secondary or tertiary libraries of the presently claimed invention.. The Office action states on page 7: "Applicant's attention is directed to Table 5, and section e) on p. 215, as an example of the approach taught in the reference. There, a primary sequence is DRYDR is used to generate a probability distribution for residues in the positions of the primary sequence which generated a list of suitable fragments upon which to model the five residue loop DRYDR. Thus, the list of fragments considered to be suitable is viewed as 'secondary library'. When smoothing template was subsequently applied, some of the modeled fragments which have been excluded from the list of suitable were then included in the list because now they appeared to fit the ranking criteria. Thus, the latter, expanded, list is viewed as a 'tertiary' library."

The single DRYDR sequence of Table 5 in Topham is not "a primary library" as asserted by the Examiner. A primary library requires a plurality of sequences, not a single sequence. The specification states: "a 'primary library' as used herein is a collection of optimized sequences, generally, but not always, in the form of a rank-ordered list" (page 9, second full paragraph). By contrast, the DRYDR sequence of Topham is a single sequence, not a "collection of optimized sequences." The list of fragments modeled on the DRYDR sequence could only be viewed as a primary library, not a secondary library as suggested by the Examiner.

Second, the claim requires "combining amino acid residues from said probability distribution at a plurality of variable positions to generate a secondary library of secondary sequences." However, amino acid residues in the sequences of the primary library are not combined to generate a secondary library. Rather, a smoothing template is applied. The smoothing template does not involve combining amino acid residues from a probability distribution. Topham therefore fails to meet this claim limitation.

Third, the claim requires a tertiary library. Topham lacks any teaching directed to a tertiary library after identifying the library in the smoothing step.

Fourth, Applicants note that the claims require "screening said tertiary library to identify at least one non-naturally occurring variant protein with said desired characteristic." Topham does not teach a non-naturally occurring variant protein.

Applicants respectfully submit that claim 10-15 are in condition for allowance.

Double Patenting

7. Claims 4-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-8 of US 6,403,312 ('312 patent) in view of alleged admitted prior art.

Without admitting or acquiescing to the Examiner's position, particularly on the issue of admitted prior art, Applicants have attached a terminal disclaimer to overcome this rejection. Applicant also confirms that the instant application and US 6,403,312 are assigned to the same assignee.

CONCLUSION

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,
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